File No. 6013-149US LGB/nt Québec, CANADA,

UNITED STATES PATENT AND TRADEMARK OFFICE

Application No	:	10/517,319	
Filing Date	:	July 15, 2005	
Applicant	:	Philippe A. Tessier	
Amended Title	:	ANTIBODIES AGAINST S100A8 AND S100A9 PROTEINS FOR MODULATING INFLAMMATORY REACTIONS	
Art Unit	:	1656	
Examiner	:	Sharon X. Wen	Tel: (571) 270-3064
Patent Agent	:	Louise G. Bernier	Tel : (418) 640-5245

Commissioner of Patents
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DECLARATION

I, **Philippe A. Tessier**, do hereby solemnly declare that:

(1) I am a citizen of Canada and am employed as an associate professor by Laval University in Québec, Canada. A copy of my curriculum vitae is enclosed in Exhibit A, enclosed herewith.

(2) I am one of the co-inventor of United States patent application serial number 10/517,319 filed on July 15, 2005.

(3) I have read and understood the content U.S. application serial number 10/517,319 as well as the Office Action of August 28, 2007.

(4) In the office action of August 28, 2007 the Examiner rejects the claims based on arguments that the activity of S100A8 and S100A9 is well known in inflammation and that it is well known that gout is an inflammatory disease. With respect, the Examiner is mixing up the intracellular activities of S100A8 and A9 involved in neutrophil degranulation *following* inflammation, a process which is well known in the art, with S100A8 and A9 secretion upon neutrophils activation in specific circumstances, leading to extracellular chemotactic activity of these two proteins, inducing inflammation and *causing* the symptoms of gout.

(5) The prior art is replete with instances where the authors have expressed skepticism about the causative role of S100A8 and A9 in inflammation. Instead, the prior art all point to the interpretation that the extracellular presence of S100A8, S100A9, and S100A12 is a consequence of inflammation, rather than a cause of inflammation (references enclosed).

(6) In support of this position, Geczy (1996) expresses clearly that:

> "Pure MRP-8 alone, or complexed with the related S100 protein MRP14, does not affect the migration of human monocytes (7) and is not active in chemotaxis assays (emphasis added) performed in parallel with CP-10" (Geczy, *Biochim. Biophys. Acta* 1313 (1996) 246-252, enclosed).

(7) The reference (7) mentioned above, discloses:

> "The recombinant or natural proteins, whether crude or partially purified, individually or in combination, did not display or inhibit (emphasis added) MIF activity..." (Odink et., *Nature* (1987), vol. 330, 80-82, enclosed).

(8) Also submitted is the reference by Frosch et al. (*Arthritis and Rheumatism* 43, pages 628-637, 2000, enclosed) which discloses the secretion of S100A8/A9 by monocytes following the interaction of monocytes with the endothelium. This references strictly teaches that secretion of S100A8 and A9 proteins is a mechanism which is *distinct* from degranulation (e.g. of other proteins). There is no teaching or suggestion from Frosch that, once S100A8 and A9 proteins are secreted by activated macrophages, such proteins may additionally act to recruit further neutrophil to the site of inflammation by chemotaxis.

(9) In support of these arguments, I also enclose the reference by Ryckman et al. (*Journal of Leucocytes Biology* 76, page 433-440, 2004) demonstrating that the secretion of S100A8/A9 by neutrophils is performed by a mechanism different than the one involved in the action of S100A8 and A9 on cell degranulation.

(10) In conclusion, it is known that:

- in the cells, S100A8 and S100A9 play a role in neutrophil degranulation;
- *but* S100A8 and S100A9 are *not* secreted upon neutrophil degranulation;
- S100A8 and S100A9 are secreted under other circumstances which have no relationship with degranulation.

(11) What was unknown:

- when secreted (i.e. extracellular), S100A8 and S100A9 play a *causative* role in inflammation by recruiting neutrophils through chemotaxis.

(12) It has now been established conclusively by my group that inhibiting these proteins in their extracellular context constitutes an effective treatment against these inflammatory reactions.

(13) I, the undersigned, declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C §1001 of the United States Code and that such willful false statements may jeopardize the validity of any patent issued for the above-referenced patent application.

Philippe A. Tessier

By: 1/22/2008 Date: